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PREPARATION OF URACILS VIA CYCLOREVERSION OF NORBORNENE-
FUSED PYRIMIDINEDIONES

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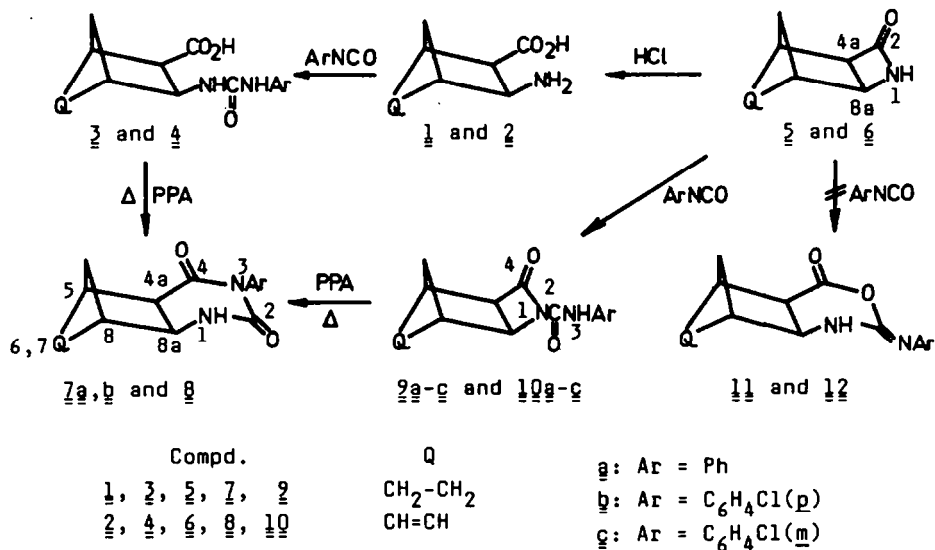
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Abstract - From diexo-norbornane- and norbornene-azetidiones 5 and 6 with aryl isocyanates, N-arylcarbamoyl-substituted β -lactams (9 and 10) were prepared. The structures of the compounds were elucidated by IR, NMR spectroscopy and X-ray analysis, in comparison with saturated methylene-bridged quinazoline-2,4-diones (7a-b) prepared from norbornane-diexo- β -amino acid (1) with isocyanates and PPA. When heated with PPA, compounds 9 can be isomerized to 7. For preparation of the unsaturated compounds 8, the amino acid 2 was converted into the acid amides (13) and cyclized with 1,1'-carbonyl-diimidazole to tricyclic quinazoline-2,4-dione (8a-g), which decompose when heated, splitting off cyclopentadiene to yield 3-substituted uracils (14).

We earlier synthesized norbornane- and norbornene-fused 1,3-oxazin-2-ones and 1,3-oxazine-2-thiones isomeric in the positions of the O and N heteroatoms,²⁻⁴ and systematically studied these compounds by NMR spectroscopy.⁵ When heated to above the melting point, the diexo and diendo norbornene-fused 1,3-heterocycles yield heteromonocycles through the splitting off of cyclopentadiene.^{6,7} By the retro Diels-Alder reaction of the methylene-bridged 2-thioxohexahydroquinazolin-4-ones prepared from 3-exo-aminobicyclo[2.2.1]hept-5-ene-2-exo-carboxylic acid and from its diendo isomer with isothiocyanates, we obtained 3-substituted thiouracils.⁸ It seemed of interest to prepare the corresponding uracils by this route, since their known syntheses are much more complicated.⁹⁻¹²

In this paper we report on the syntheses of norbornane- and norbornene-fused pyrimidine-2,4-diones, the isomeric N-substituted β -lactams obtained from the norbornane- and norbornene-azetidiones and the uracils obtained by thermolysis of the norbornene-fused pyrimidine-2,4-diones prepared by cyclization of the amino acid amides.

When boiled in chlorobenzene with PPA, the ureas 3 obtained from 3-*exo*-amino-bicyclo[2.2.1]heptane-2-*exo*-carboxylic acid² (1) and isocyanates were cyclized to 3-aryl-5,8-methano-3,4,4a,c-5,6,7,c-8,c-8a-octahydroquinazoline-2,4-diones (7a and b) (Scheme 1). Due to the low solubility of the 5,6-unsaturated di-*exo*- β -amino acid¹⁴ (2), this method proved unsuitable for preparation of the analogue 8. Without solvent, however, an *N*-biscarbamoyl amino acid derivative was formed.



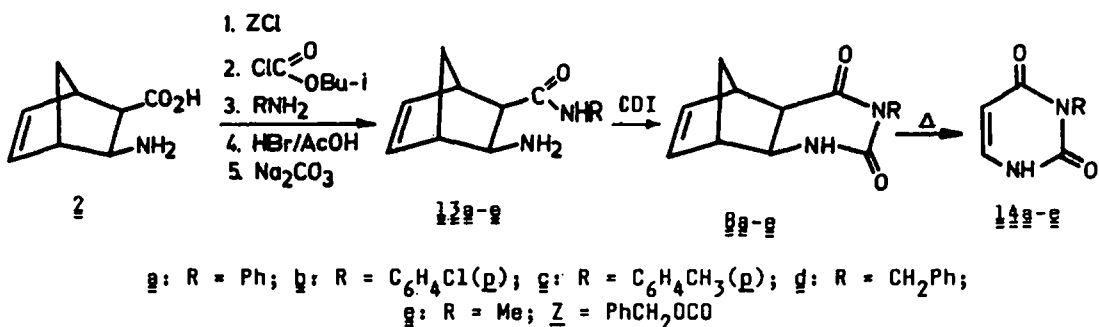
Scheme 1

We therefore attempted the syntheses of the pyrimidinediones 7 and 8 from the norbornane- and norbornene-fused azetidinones (5 and 6), which are the precursors of the corresponding β -amino acids. Of the β -lactams, the unsaturated 6 has already been used successfully in ring transformation with imidates for the synthesis of 2-substituted pyrimidin-4-ones.⁷ The di-*exo*-3-aza-4-oxotricyclo[4.2.1.0]nonane (5) and non-7-ene (6) were prepared from norbornene and norbornadiene through chlorosulphonyl isocyanate cycloaddition^{13,14} and subsequent reduction with sulphite.¹⁵

In principle, the formation of the structural isomers 7-8, 9-10 or 11-12 is possible from the azetidinones 5 and 6 with aryl isocyanates, the structures were determined by IR, NMR and X-ray methods.

When heated in PPA, the *N*-substituted saturated azetidinone (9a) was converted into pyrimidine-2,4-dione (7a). This process can be regarded as an intramolecular transacylation, when the more stable pyrimidinedione structure comes into being from the strained azetidinone ring. The similar rearrangement of the isomeric imino-1,3-oxazines is known, *i.e.* the conversion of iminobenzoxazines (obtained from anthranilic acid with isocyanates) into quinazolinone by heating with PPA.¹⁶ However, we did not succeed in isomerizing the unsaturated derivatives 10 with PPA into pyrimidine-2,4-diones (8).

To obtain compounds 8, therefore, the amino group of the 3-*exo*-aminobicyclo[2.2.1]hept-5-ene-*exo*-carboxylic acid¹⁴ (2) was protected by benzyloxycarbonylation (Z-group) and with isobutyl chloroformate a mixed anhydride was prepared, the aminolysis of which results in carboxamides. After removal of the protecting group with hydrogen bromide-glacial acetic acid, compounds 13 were cyclized with 1,1'-carbonyldiimidazole to the norbornene-fused pyrimidine-2,4-diones (8a-8) (Scheme 2).



Scheme 2

When melted, the tricyclic pyrimidine-2,4-diones ($\underline{9a-g}$) decomposed: cyclopentadiene was split off and the heteromonocycles $\underline{14a-g}$ were formed; the latter were isolated by purification of the reaction mixture on a silica gel column.

The importance of our alternative method is that the 3-uracils can be obtained in a clear-cut, simpler way than in other methods.⁹⁻¹² The m.p. of the 3-methyluracil obtained by methylation¹⁷⁻¹⁹ (179 °C¹⁷, 176 °C¹⁸, 189.5-191 °C¹⁹) is practically identical with that of our compounds $\underline{14e}$ (175-177 °C), and the m.p. for our 3-phenyluracil (246-247 °C) agrees with the lit. m.p. (246-247⁹ and 242-246^{11,12}), as does that for our 3-*p*-tolyluracil (256-258 °C) with the lit. m.p. (234-235 °C⁹).

Structure proof by IR and NMR spectroscopy

According to Scheme 1, both reaction paths can, in principle, lead to the formation of the compound types $\underline{7-8}$, $\underline{9-10}$ and $\underline{11-12}$. We therefore attempted to elucidate the structures by means of IR, ¹H and ¹³C NMR spectroscopy (Tables 1 and 2). (For comparison of the spectral data on the analogues, the numbering in compounds $\underline{5}$, $\underline{6}$, $\underline{7}$ and $\underline{10}$ is shown in Scheme 1.)

The structures of the pyrimidinediones $\underline{7}$ and $\underline{8}$ appear probable, both from the manner of preparation (isocyanate, PPA) and from the IR bands characteristic of coupled carbonyl vibrations²⁰ and differing characteristically in intensity. By reason of the relatively low νC=O IR frequency, the *N*-carbamoyl-β-lactam structure can be ruled out. However, the structures $\underline{11}$ and $\underline{12}$ can not be precluded on the evidence of the IR data alone, since the "carbonyl" band appearing at lower wavenumbers may originate from the νC=N bond, too. At the same time, the chemical shift of the C-2 line (152.3-153.7 ppm) corresponds to the value expected for the sp² carbon atom linked to the three heteroatoms. However, the carbon shifts of the aryl substituent are unambiguous evidence against structures $\underline{11-12}$ (and also against structures $\underline{9-10}$), for in these (due to the electron-donor NH group and the conjugating C=N bond) a significant upfield shift of the C-2',4',6' lines would be expected; in fact, this can be observed for compounds $\underline{7}$ and $\underline{10}$ (cf. Table 2).

At the same time, the structures $\underline{9-10}$ and $\underline{11-12}$ can not be differentiated on this basis. For the carbamoyl-β-lactams $\underline{7}$ and $\underline{10}$, the two carbonyl bands are shifted towards higher frequencies, the distance between them is increased and their intensities tend to equalize. (Instead of 1709-1724 and 1670-1688 cm⁻¹, characteristic for compounds $\underline{7-8}$, the two bands are found in the ranges 1749-1769 and 1697-1713 cm⁻¹.) These observations support the structure, as for $\underline{9-10}$ no coupling of the carbonyl frequencies (the favourable "W"-type arrangement of the CONCO group is impossible) and hence no great differences in intensity and equalization in frequency are to be expected for the two bands. The frequency

Table 1. IR frequencies^a and ¹H NMR data for compounds 5-10 and 14^b

Compd.	¹ H NMR/shifts								ArH (R) 1-4 signal (4/5 H)	CH _{2/3} s(2/3H)
	H-4a d ^e (1H)	H-8a d ^e (1H)	H-5 ms ^f (1H)	H-8/6 ^g ms ^f (1H)	NH(1) s(1H)	H-6,7 m/dd(2/4H) ^h	H-9 2xd(2x1H) ⁱ			
<u>5</u>	2.95	3.37		2.37	~6.0	~1.05, 1.5-1.75	1.21, ~1.6		-	-
<u>6</u>	3.04	3.49	2.89	2.92	6.65	6.12, 6.24	1.64, 1.80		-	-
<u>7a</u>	2.81	3.45	2.27	2.81	5.95		1.2-1.8		7.14 ^j , ~7.4 ^k	-
<u>7b</u>	2.78	3.45	2.25	2.86	7.95		1.2-1.6		7.15 ^l , 7.42 ^l	-
<u>8a</u>	2.67	3.35	3.17	2.92	8.12	6.20, 6.37	1.47 1.63		~7.1 ^l , ~7.4 ^k	-
<u>8b</u>	2.66	3.34	3.17	2.91	8.17 ^m	6.20 6.37	1.46 1.63		7.15 ^l , 7.45 ^l	-
<u>8c</u>	2.75	3.46	3.40	2.93	6.15	6.13 6.37	1.62 1.75		7.03 ^l , 7.25 ^l	2.38
<u>8d</u>	2.62	3.36	3.34	2.85	6.29	6.10 6.34	1.47 1.50		7.2-7.4	4.99
<u>8e</u>	2.62	3.41 ⁿ	3.35	2.95	6.98	6.14 6.36	1.54		-	3.20
<u>9a</u>	3.08	3.92	2.53	2.84	8.53	~1.15, 1.6-1.7	1.35, 1.55		7.09 ^o , 7.32 ^p 7.50 ^q	-
<u>9b</u>	3.10	3.92	2.53	2.83	8.54	~1.15, 1.6-1.7	1.34 ^q , 1.54 ^q		7.27 ^l , 7.43 ^l	-
<u>9c</u>	3.10	3.92	2.54	2.83	8.55	~1.15, 1.6-1.7	1.35, 1.53		7.05 ^r , 7.22 ^s 7.33 ^t , 7.62 ^u	-
<u>10a</u>	3.14 ^v	3.98	3.06	3.37	8.52	6.20 6.29	1.63, 1.72		7.09 ^o , 7.32 ^p 7.50 ^q	-
<u>10b</u>	3.16	4.00	3.08	3.38	8.54	6.21 6.31	1.62, 1.74		7.28 ^l , 7.45 ^l	-
<u>10c</u>	3.16	4.00	3.08	3.38	8.56	6.21 6.31	1.61, 1.74		7.07 ^r , 7.23 ^s 7.32 ^t , 7.64 ^u	-
<u>14a</u>	-	-	5.68	7.51	11.3	-	-	-	~7.2 ^j , ~7.4 ^k	-
<u>14b</u>	-	-	5.68	7.51	11.3	-	-	-	7.26 ^l , 7.51 ^l	-
<u>14c</u>	-	-	5.66	7.50	11.2	-	-	-	7.08 ^l , 7.24 ^l	2.34
<u>14d</u>	-	-	5.77 ⁿ	7.08 ⁿ	10.2	-	-	-	7.27 ^k , 7.45 ^j	5.10
<u>14e</u>	-	-	5.81 ⁿ	7.24 ⁿ	10.5	-	-	-	-	3.34

^a KBr, $\nu_{C=O}^c$, ν_{NH}^d (Compd.): 1735, 3190 (5), 1735, 3198 (6), 1718, 1680, 3260 (7a), 1724, 1688, 3325 (7b), 1720, 1678, 3225, 3099 (8a), 1724, 1688, 3223, 3101 (8b), 1720, 1678, 3217, 3098 (8c), 1709, 1672, 3244 (8d), 1715, 1670, 3236, 3103 (8e), 1749, 1703, 3310 (9a), 1761, 1697, 3315 (9b), 1749, 1711, 3310 (9c), 1763, 1699, 3330 (10a), 1769, 1697, 3310 (10b), 1753, 1713, 3300, 3290 (10c), 1736, 1635, 3230 (14a), 1742, 1635, 3250 (14b), 1740, 1640, 3234 (14c), 1730, 1707, 1630, 1605, 3090 (14d), 1705, 1630, 3190 (14e). ^b ¹H NMR in CDCl₃ solution, $\delta_{TMS} = 0$ ppm at 250 MHz; for 8a, b and 14a-c in DMSO-*d*₆ solution. ^c For 7a, b, 8a-e and 14a-e the carbonyl band at lower wave numbers is more intense: both bands are split in the case of 14d. ^d Sharp; for 14a-e broad, split for 8a-c, e and 10c. ^e $J(4a, 8a)$: 3.6 (5), 3.8 (6), 8.8 (7a, b and 8b, c, e), 8.7 (8a), 8.9 (8d), 4.0 (9a-c), 4.4 (10a, b) and 4.2 Hz (10c). ^f Doublet for 9a-c and 14a-c, split by 2.3-3.0 (9a-c) and 7.7 Hz (14a-e), resp.; singlet-like signals of d with coalesced lines for 5, 6, 7a, b, 8a-e and 10a-c. ^g H-6 for (14a-e), H-8 in all other cases. ^h In the spectra of 7a, b overlapped with the H-9 signal, in the case of 5 and 9a-c the upfield signal of 2H-intensity is approximately a dd, the downfield one an unresolved m (2H), for 6, 8a-e and 10a-c two dd with $J(6,7)$: 5.6 Hz, $J(5,6) \neq J(7,8)$: 3.0-3.3 Hz. ⁱ AB spectrum, $J(A,B)$: 9.4-11.0 Hz, in the case of 7a, b coalesced with the m of H-6,7. One of the d overlapped with the downfield m of H-6,7 in the spectrum of 5, $\delta_A = \delta_B$ for 8d, e. ^j H-2', 6' dd (2H). ^k H-3', 5' m (3H). ^l A or B part (2x2H) of an AA'BB' multiplet, $J(A,B) = 9$ Hz. ^m Doublet, $J(NH-1, H-8a)$: 1.7 Hz. ⁿ Further d splitting (due to coupling with the NH group) by 1.5 (8e and 14e, H-5) 1.0 (14d, H-5) and 5.7 Hz, (14d, e, H-6), resp. ^o H-4', dt (1H). ^p H-3', 5', dt, (2H). ^q All lines of the AB quartet show a further t split by ~1 Hz. ^r H-4', dd (1H). ^s H-5', t, (1H), split by 7.9 Hz. ^t H-6', dd (1H). ^u H-2', t (1H), split by 2.0 Hz. ^v Both lines of d split to further t's by 1.4 Hz.

Table 2. ^{13}C NMR chemical shifts of compounds $\underline{5}$ - $\underline{10}$ and $\underline{14}$ ^{a, b}

Compd.	C-2	C-4	C-4a	C-5	C-6 ^c	C-7	C-8	C-8a	C-9	C-1'	C-2' C-6'	C-3' C-5'	C-4, ^d
$\underline{5}^e$	-	169.2	52.2	32.9	25.9	24.0	37.2	57.4	29.8	-	-	-	-
$\underline{6}^e$	-	170.6	52.5	38.3	137.7	135.6	43.3	57.6	40.3	-	-	-	-
$\underline{7a}$	152.7	170.5	47.3	44.5	29.2	25.1	46.1	54.5	33.5	135.4	128.9 ^f	-	-
$\underline{7b}$	152.3	170.4	47.4	43.8	29.3	25.1	46.3	54.7	33.7	134.4	130.3	129.2	133.8
$\underline{8a}$	153.3	171.6	51.9 ^g	45.0 ^h	140.0	137.1	50.1 ^g	52.6 ^g	43.5 ^h	138.0	131.2	130.0	129.1
$\underline{8b}$	153.1	171.6	52.0 ^g	45.0 ^h	140.0	136.8	50.6 ^g	52.5 ^g	43.8 ^{h, i}	137.0	132.7	130.0	133.9
$\underline{8c}$	153.7	172.0	52.0 ^g	45.1 ^h	140.3	137.3	50.2 ^g	52.7 ^g	43.7 ^h	135.5	130.7 ^f	-	138.7
$\underline{8d}$	153.2	170.0	50.8 ^g	42.5	139.0	135.2	49.1 ^g	51.7 ^g	43.7 ^h	137.9	128.4 ^j	128.5 ^j	127.3
$\underline{8e}^e$	153.6	170.4	50.7 ^g	42.4	139.1	135.1	49.0 ^g	51.9 ^g	43.7	-	-	-	-
$\underline{9a}$	147.1	168.1	55.9 ^g	34.1	26.6	23.9	36.6	56.2 ^g	30.8	137.1	119.2	128.5	123.5
$\underline{9b}^e$	147.4	168.7	56.7 ^g	35.7	27.0	24.3	36.9	56.4 ^g	31.2	135.9	120.8	128.9	129.1
$\underline{9c}$	147.5	168.9	56.6 ^g	34.7	27.1	24.5	37.1	56.9 ^g	31.3	138.7	119.9 111.7	134.9 130.0	124.2
$\underline{10a}$	147.4	168.9	55.8 ^g	39.4	138.0	135.8	42.5	56.0 ^g	40.8	137.1	119.5	128.8	123.9
$\underline{10b}^e$	147.7	169.3	56.2 ^g	39.8	138.3	136.1 ^k	42.3	56.4 ^g	41.1	136.1 ^k	121.0	129.1	129.3
$\underline{10c}$	147.2	168.9	55.9 ^g	39.4	138.0	135.7	42.5	56.1 ^g	40.7	138.4	119.5 117.4	134.5 129.7	123.8
$\underline{14a}$	153.1	164.9	-	102.0	142.8	-	-	-	-	137.2	130.5 ^f	-	129.6
$\underline{14b}$	152.9	164.7	-	101.9	142.9	-	-	-	-	136.0	132.4	130.4	134.2
$\underline{14c}^e$	153.2	165.0	-	102.0	142.8	-	-	-	-	134.0	131.0	130.2	139.1
$\underline{14d}$	153.3	164.8	-	101.6	142.5	-	-	-	-	139.1	130.0	129.3	128.8
$\underline{14e}$	153.3	165.0	-	101.3	141.9	-	-	-	-	-	-	-	-

^a In COCl_2 solution; $\underline{8a}$ - \underline{c} and $\underline{14a}$ - \underline{e} in DMSO-d_6 solution; $\delta_{\text{TMS}} = 0$ ppm. ^b At 20.15 MHz; for $\underline{8c}$, \underline{d} and $\underline{14b}$ at 62.89 MHz. ^c $\text{CH}_3/2$ signals: 22.3 ($\underline{8c}$), 43.6^h ($\underline{8d}$), 27.2 ($\underline{8e}$), 22.4 ($\underline{14c}$), 44.4 ($\underline{14d}$) and 28.0 ($\underline{14e}$). ^{c, g, h, j} Reversed assignments may also be possible. ^e Assignments were confirmed by DEPT measurements. ^f Two overlapping lines. ⁱ Hidden by the solvent signal. ^k Two overlapping lines, confirmed by proton-coupled spectrum.

increase observed can readily be interpreted in terms of the mutual electron-withdrawing effect of the two carbonyl groups.

The chemical shift of the H-8a atom is significantly higher than for compounds $\underline{7}$ - $\underline{8}$ (instead of 3.35-3.45 ppm, its value is 3.92-4.00 ppm), since the neighbouring electron-donor NH group is replaced by imide nitrogen with a strong -I effect. This is further support for the structures, because it is likewise evidence against structures $\underline{11}$ - $\underline{12}$. On the other hand, the significant upfield shift of the C-2 line (~ 6 ppm) as compared to the positions for isomers $\underline{7}$ - $\underline{8}$ can readily be reconciled with structures $\underline{11}$ - $\underline{12}$, too. The decisive argument for the β -lactam structure (four-membered ring) is the value of the H-4a, H-8a coupling constant, 4.0-4.4 Hz, for $\underline{9}$ - $\underline{10}$; this is similar to those measured for $\underline{5}$ - $\underline{6}$ (3.5 and 3.8 Hz), but is about half those for the quinazolinones $\underline{7}$ - $\underline{8}$ (8.8-8.9 Hz). The small coupling constant for the azetidinones follow above all from the reduced electron density around the C-4a, 8a atoms.²¹

The structures $\underline{7}$ - $\underline{8}$ can be considered proved by the IR and NMR data, while the structures $\underline{9}$ - $\underline{10}$ are only rendered probable by comparison of the data on the com-

pounds in the two different types of series. For final evidence, we performed an X-ray analysis of $\underline{10c}$.

In earlier work on other fused heterocycles, we dealt in detail with the spectroscopic characterization of the norbornane and norbornene skeletons.^{5,22,23} Thus, we have not mentioned these data here, but of course the confirmation of the assumed structures $\underline{5-10}$ necessarily involves the spectral data on the carbocyclics listed in Tables 1 and 2, too. Their lack unequivocally confirm the structures of the uracils $\underline{14a-g}$.

X-ray analysis of $\underline{10c}$

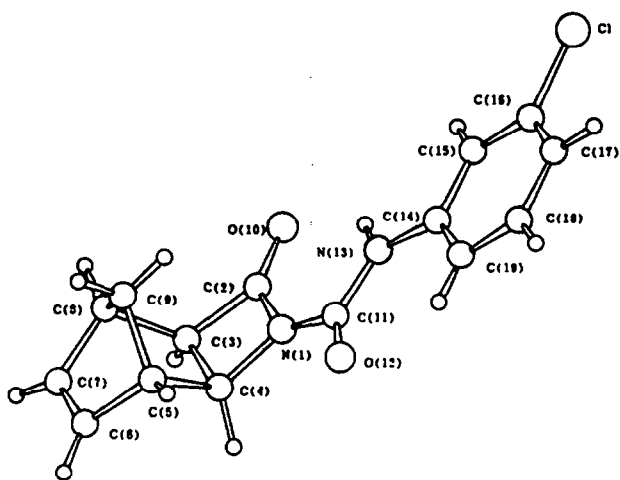


Fig. 1. A perspective view of the molecular structure of $\underline{10c}$

The X-ray structure depicted in Fig. 1. corresponds to the chemical constitution of a carbamoyl β -lactam. The azetidinone ring is planar; its best plane forms a dihedral angle of $64.5(2)^\circ$ with that of the C(3),C(4),C(5),C(8) moiety pertaining to the norbornane skeleton. The latter comprises a six-membered ring having an almost perfect boat form, with the puckering parameters²⁴ $Q = 0.990(3) \text{ \AA}$, $\Psi = 120.8(2)$. $\Theta = 90.6(2)^\circ$, and two five-membered rings of nearly ideal envelope shape [$Q = 0.586(3)$, $0.544(3) \text{ \AA}$, $\Psi = 287.2(3)$, $144.0(4)^\circ$], with C(9) on the common flap. The least squares plane of the phenylcarbamoyl group [including the non-H atoms from C(11) to

C(19)] is slightly inclined to that of the azetidinone ring [the corresponding dihedral angle is $10.9(1)^\circ$]. On these quasicoplanar planes, a delocalized $p\pi$ - $p\pi$ bond system is formed with C-N bonds, the lengths of which vary in the range 1.38-1.42 \AA . The phenylcarbamoyl- β -lactam system contains two intramolecular hydrogen-bonds. The stronger is formed between N(13)-H(13) as donor and O(10) as acceptor [$N\dots O = 2.909(2) \text{ \AA}$, $H\dots O = 2.099(2) \text{ \AA}$, $\angle NH\dots O = 141.5(3)^\circ$], whilst the weaker is a CH...O type involving C(19), H(19) and O(12) with the parameters $C\dots O = 2.869(2) \text{ \AA}$, $H\dots O = 2.252(2) \text{ \AA}$, $\angle CH\dots O = 121.9(4)^\circ$. The molecules related by twofold-screw-axes are linked by infinite chains of rather weak hydrogen-bonds $/N(13)\dots O(10)[1-x, y+1/2, 3/2-z] = 3.556(2) \text{ \AA}$, $H(13)\dots O(10)[1-x, y+1/2, 3/2-z] = 2.845(2) \text{ \AA}$, $\angle NH\dots O = 131.9(3)^\circ$.

EXPERIMENTAL

General methods

M.p.s are uncorrected. IR spectra were run in KBr discs on a Bruker IFS-113v FT spectrometer equipped with an Aspect 2000 computer. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 solution in 5 or 10 mm tubes, at room temperature, on a Bruker WM-250 (^1H) or a WP 80-SY (^{13}C) FT spectrometer controlled by an Aspect 2000 computer at 250.13 (^1H) and 20.14 (^{13}C) MHz, respectively, using the

deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: sweep width 5 kHz, pulse width 1 and 3.5 μ s ($\sim 20^\circ$ and $\sim 30^\circ$ flip angle), acquisition time 1.64 s, number of scans 2⁴ and 2⁸-2¹⁷, computer memory 16 K. Complete proton noise decoupling (~ 1.5 W) for the ¹³C spectra, and Lorentzian exponential multiplication signal-to-noise enhancement, were used (line width 0.7 and 1.0 Hz).

DEPT experiments²⁵ were performed in a standard way,²⁶ using only the $\theta = 135^\circ$ pulse to separate CH/CH₃ and CH₂ lines phased "up" and "down", respectively. Typical acquisition data were: number of scans 128-12 K, relaxation delay for protons 3 s, 90^o, pulse width 10.8 and 22.8 μ s for ¹³C and ¹H, respectively. The estimated value for $J(C,H)$ resulted in a 3.7 ms delay for polarization.

Preparation of N-3-exo-carboxybicyclo[2.2.1]heptyl-2-exo-N'-arylureas (7a,b)

3-exo-Aminobicyclo[2.2.1]heptane-2-exo-carboxylic acid² (1.55 g; 0.01 mol), abs. EtOH (50 ml) and isocyanate (1.19 g phenyl isocyanate or 1.53 g p-chlorophenyl isocyanate; 0.01 mol) were refluxed together for 2 h. The mixture was evaporated and the residue was crystallized from EtOH. 7a: m.p. 207-209 °C (decomp.), yield 1.83 g (67%). (Found: C, 65.54; H, 6.75; N, 10.30. C₁₅H₁₈N₂O₃ requires C, 65.68; H, 6.61; N, 10.21%.)

Preparation of 3-aryl-5,8-methano-3,4,r-4a,c-5,6,7,c-8,c-8a-1H-octahydroquinazoline-2,4-diones (7a,b)

7a or b, prepared as above, PPA (5.0 g) and chlorobenzene (30 ml) were refluxed together for 10 min. After filtration, the mixture was evaporated to dryness and the residue was recrystallized from nitromethane. Data on compounds 7a,b are listed in Table 3.

Table 3. Physical and analytical data for compounds 7a,b, 8a-g, 9a-c, 10a-c and 14a-g

Compd.	M.p. (°C)	Yield (%)	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
7a	228-230	42	70.31	6.40	10.97	C ₁₅ H ₁₆ N ₂ O ₂	70.23	6.29	10.93
7b	295-296	48	62.00	5.34	9.68	C ₁₅ H ₁₅ N ₂ ClO ₂	61.97	5.20	9.63
8a	218-220 ^{a,b}	78	70.89	5.70	11.20	C ₁₅ H ₁₄ N ₂ O ₂	70.85	5.55	11.02
8b	231-233 ^{a,c}	82	62.52	4.47	9.73	C ₁₅ H ₁₃ N ₂ ClO ₂	62.40	4.54	9.70
8c	227-229 ^{a,b}	75	71.81	6.08	10.35	C ₁₆ H ₁₆ N ₂ O ₂	71.62	6.01	10.44
8d	182-183 ^b	85	71.75	6.14	10.32	C ₁₆ H ₁₆ N ₂ O ₂	71.62	6.01	10.44
8e	197-199 ^{a,b}	67	62.33	6.42	14.71	C ₁₀ H ₁₂ N ₂ O ₂	62.49	6.29	14.57
9a	124-126 ^b	67	70.41	6.21	10.84	C ₁₅ H ₁₆ N ₂ O ₂	70.29	6.29	10.93
9b	117-119 ^b	63	62.10	5.33	9.53	C ₁₅ H ₁₅ N ₂ ClO ₂	61.97	5.20	9.63
9c	150-152 ^b	70	62.09	5.40	9.57	C ₁₅ H ₁₅ N ₂ ClO ₂	61.97	5.20	9.63
10a	112-114 ^b	62	70.79	5.63	10.91	C ₁₅ H ₁₄ N ₂ O ₂	70.85	5.55	11.02
10b	112-114 ^b	62	62.48	4.56	9.78	C ₁₅ H ₁₃ N ₂ ClO ₂	62.40	4.54	9.70
10c	155-157 ^b	65	62.27	4.70	9.54	C ₁₅ H ₁₃ N ₂ ClO ₂	62.40	4.54	9.70
14a	246-247 ^{d,e}	85				C ₁₀ H ₈ N ₂ O ₂			
14b	267-269 ^d	82	53.96	3.31	12.47	C ₁₀ H ₇ N ₂ ClO ₂	53.95	3.17	12.58
14c	256-258 ^{b,f}	80				C ₁₁ H ₁₀ N ₂ O ₂			
14d	182-183 ^b	80	65.48	4.89	14.04	C ₁₁ H ₁₀ N ₂ O ₂	65.34	4.98	13.85
14e	175-177 ^{b,g}	65				C ₅ H ₆ N ₂ O ₂			

^a Decomp. ^b Crystallized from EtOH. ^c From dioxan. ^d From 70% EtOH. ^e Lit. m.p. 246-247 °C⁹ and 242-245 °C.^{11,12} ^f Lit. m.p. 234-235 °C.⁹ ^g Lit. m.p. 179 °C,¹⁷ 176 °C¹⁸ and 189.5-191 °C.¹⁹

Preparation of 3-arylcarbamoylaza-4-oxotetracyclo[4.2.1.0]nonane (2a-c) and 3-aryl-carbamoylaza-4-oxotetracyclo[4.2.1.0]non-7-ene (10a-c)

Diexo-3-aza-4-oxotetracyclo[4.2.1.0]nonane (5) (1.35 g; 0.01 mol) or -non-7-ene (6), isocyanate (1.19 g phenyl isocyanate, or 1.53 g *m*- or *p*-chlorophenyl isocyanate; 0.01 mol), EtOH saturated with HCl (one drop) and abs. chlorobenzene (20 ml) were refluxed together for 12 h. After evaporation, the residue was dissolved in benzene (20 ml), transferred onto a silica gel column, and eluted with benzene and subsequently with ethyl acetate. In the case of 2 the benzene eluate, and in the case of 10 the ethyl acetate eluate, was evaporated and the residue was crystallized from EtOH. Data on compounds 2a-c and 10a-c are listed in Table 3.

Conversion of 2a to 7a

2a (1.0 g) and PPA (30 ml) were heated together for 3 h at 150 °C. The cooled mixture was then poured into water (100 ml), and the solution was filtered and extracted with CHCl₃ (3x50 ml). After washing with water and drying (Na₂SO₄), the solvent was distilled off and the residue was eluted with benzene from a silica gel column. The residue (0.30 g) was crystallized from EtOH, m.p. 228-230 °C. The compound was identified by IR, by comparison with 7a.

Preparation of 3-substituted-5,8-methano-3,4,r-4a,c-5,c-8a,c-8a-hexahydro-quinazoline-2,4-diones (8a-e)

Carboxamide 13²⁷ (2.28 g 13a, 2.63 g 13b, 2.42 g 13c,d or 1.66 g 13e; 0.01 mol) and 1,1'-carbonyldiimidazole (6.48 g; 0.04 mol) in dry benzene (30 ml) were refluxed together for 8 h. After cooling, water (20 ml) was added dropwise under stirring, and the solid separating out was filtered by suction. The mother liquor was extracted with benzene (3x20 ml) and the extract was evaporated after drying (Na₂SO₄). The combined solid plus residue was crystallized. Data on compounds 8a-e are listed in Table 3.

Preparation of 3-substituted uracils (14a-e)

Compound 8 (1.0 g) was heated for 10 min to a temperature about 10 °C higher than the m.p. of the compound. After the mixture had cooled, the residue was dissolved in ethyl acetate, transferred onto a silica gel column and eluted with ethyl acetate. The solvent was evaporated off and the product was crystallized. Data on compounds 14a-e are shown in Table 3.

X-ray crystal structure determination of 10c

Crystal data: C₁₅H₁₃N₂ClO₂, M_r = 288.74, monoclinic, *a* = 13.842(1), *b* = 5.753(1), *c* = 20.811(3) Å, β = 125.13(1)°, U = 1355.4(7) Å³, Z = 4, D_c = 1.415 g.cm⁻³, F(000) = 600, space group P2₁/c, μ = 25.43 cm⁻¹ for CuKα radiation (λ = 1.54184 Å). Dimensions of the crystal sample: 0.05 x 0.15 x 0.30 mm³. Intensities of 2284 unique reflections were collected on an Enraf-Nonius CAD-4 diffractometer equipped with a graphite monochromator in the range 1.5 < 2θ < 75.0° by an ω-2θ scan. Cell constants were determined by least-squares refinement of 25 reflections. After data reduction, 1608 reflections with I > 3.0σ(I) were taken as observed. The phase problems were solved by direct methods, using the MULTAN 82 program.²⁸ In the course of the isotropic least-squares refinement of the positional parameters of non-hydrogen atoms, an empirical absorption correction was calculated with the DIFABS²⁹ program. The minimum and maximum corrections were 0.782 and 1.266. The fractional coordinates of hydrogen atoms bound to carbon atoms were

Table 4. Fractional coordinates of non-hydrogen atoms for $10\bar{c}^x$

	x/a	y/b	z/c
C120	0.4477(1)	0.2526(2)	0.9179(0)
O10	0.4540(1)	-0.6714(4)	0.7223(1)
O12	0.0902(1)	-0.5645(4)	0.6350(1)
N1	0.2505(2)	-0.7405(5)	0.6531(1)
N13	0.2758(2)	-0.4214(4)	0.7274(1)
C2	0.3639(2)	-0.7683(6)	0.6729(1)
C3	0.3243(2)	-0.9503(5)	0.6097(1)
C4	0.1980(2)	-0.9145(5)	0.5888(1)
C5	0.1276(2)	-0.8176(6)	0.5045(1)
C6	0.1238(2)	-1.0188(6)	0.4562(1)
C7	0.2307(2)	-1.0455(5)	0.4734(1)
C8	0.3095(2)	-0.8629(6)	0.5337(1)
C9	0.2209(3)	-0.6666(6)	0.5075(1)
C11	0.1965(2)	-0.5705(6)	0.6701(1)
C14	0.2504(2)	-0.2344(5)	0.7589(1)
C15	0.3462(2)	-0.1026(6)	0.8160(1)
C16	0.3274(2)	0.0864(6)	0.8482(1)
C17	0.2158(2)	0.1483(6)	0.8248(1)
O18	0.1224(2)	0.0150(7)	0.7688(2)
O19	0.1377(2)	-0.1755(6)	0.7355(1)

*e.s.d's in parantheses

generated from assumed geometries, while that of the NH group was located in a difference Fourier map. The hydrogen positions were only included with a mean isotropic temperature factor (fixed as the B_{eq} of the adjacent atom $+1 \text{ \AA}^2$) in the structure factor calculations. Final $R = 0.042$, $R_w = 0.038$, $R_{int} = 0.068$, $S = 3.04$, $W = 4F^2/\sigma^2(F_0^2)$. The highest peak in the final difference Fourier map was $0.21(3) \text{ e.\AA}^{-3}$. Scattering factors were taken from standard tables.³⁰ All calculations were performed on a PDP 11/34 minicomputer with the use of the SDP system of Enraf-Nonius with local modifications. Fractional coordinates for non-hydrogen atoms are given in Table 14.

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